REMARKS

Claims 1-16 were pending. Claims 1-3 are amended herein. Support for the amendments are found throughout the specification, *e.g.*, page 9, lines 6-13. The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future applications. Claims 1-16 are presently pending. No claim has been allowed.

Formal Matters

Applicants gratefully acknowledge the entry of the Request for Continued Examination and the entry of the amendments to the claims filed in Papers No. 17 and 21.

With respect to Paper 22, ¶5, Applicants note that the language of the pending claims indicate that the tumor cells to be treated using the claimed methods are those resulting from metastasis. While metastatic tumors can encompass a primary tumor with metastatic cells as well as tumors arising in distant sites following metastasis, the language of the pending claims distinguishes between these possibilities. A primary tumor is by definition not one that arises from metastasis. *See* Exhibit A. Therefore, while the specification contemplates the methods as a means for treating either primary disease or residual metastatic disease, the methods of claims 1 and 2 are drawn to the treatment of metastatic disease.

Applicants appreciate the withdrawal of the objection and rejection set forth in Paper No. 16.

The Action objects to the specification because of the alleged use of numerous improperly demarcated trademarks were noted in the specification. The specification is amended herein.

Applicants have also amended the specification to delete embedded hyperlinks and correct minor typographical errors.

In view of the above, Applicants respectfully request the withdrawal of the objection.

Rejection under 35 U.S.C. §103 (a)

Claims 1-16 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 6,290,712-B1 (hereinafter the '712 patent) in view of U.S. Patent Nos. 4,436,727, 4,912,094, 5,149,527, 5,579,554, 5,747,475, 5,770,619, 6,929,105, 5,990,149, 6,071,944, and 6,149,671 and Momma et al., Fischer et al., Karrer et al., Lapeš et al., and van Hillegersberg et al. for reasons of record. Applicants respectfully traverse this rejection.

1. There is no motivation to combine the cited references.

Applicants respectfully submit that one of ordinary skill in the art would not be motivated to combine the '712 patent with other references disclosing green porphyrins because the '712 patent discloses a subset of chromophores that are distinct and non-overlapping with the green porphyrins of U.S. Patent No. 5,770,619, 5,990,149, 5,929,105, and Momma et al. Green porphyrins, and their characteristics, *e.g.*, eliciting cell death in the absence of appreciable heating in the tissues, is a critical element of the instant methods which clearly distinguishes it from the prior art references for at least the reasons discussed below. *See Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987) ("Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored.").

First, differences in the activation wavelength of a photosensitizer substantially affect the therapeutic outcome of photodynamic therapy, and therefore a teaching or disclosure regarding a positive therapeutic outcome at one activation wavelength offers no guidance or motivation regarding another wavelength. *See, e.g.*, Exhibit B at page 155 ("Because light penetration decrease exponentially as a function of distance, adjustments of relatively few nanometers in activation wavelength can lead to potentially substantial increases in therapeutic outcome."). The '712 patent discloses desired chromophores as having "strong absorption in the red and near-infrared spectral region for which tissue is relatively transparent" with a preferred wavelength of 808 ± 10 nm. *See* column 7, lines 43-47. The red and near-infrared spectral region is 700-2000 nm. Green porphyrins, on the other hand, are activated in the range of 550 to 695 nm, a wavelength in the visible portion of the spectral region. *See* specification, at page 27, lines 16-19. Because just a

small change in the activation wavelength can dramatically effect the therapeutic outcome, it is not obvious to the skilled artisan that results achieved with a photosensitizer activated at 808 nm teach or suggest the results with a chemically-unrelated photosensitizer activated at 690 nm. Therefore, for both the '712 patent and US Patent No. 6,071,944, the disclosure of photosensitizers with activation wavelengths distinct from that of green porphyrin provides no motivation regarding the use of green porphyrins as claimed in the instant methods.

Second, the skilled artisan would not be motivated to combine the teachings of the '712 patent using the higher activation wavelength and photosensitizers that mediate cell destruction via a photothermal-mediated cell death with references disclosing green porphyrins because porphyrins mediate cell death through a distinct process that does not require any appreciable heat generation. It is well-known in the art that heat "insults" cells and elicits various response, ranging from cytokine production, activation of various lymphocytes and phagocytes to vascular damage. The '712 patent repeatedly emphasizes that the reduction in tumor cells is achieved through this photothermal effect. *See, e.g.*, column 6, lines 4-7 ("When photothermal destruction occurs, the fragmented tissue and cellular molecules are disbursed within the host in the presence of immunologically potentiating material ..."); column 6, lines 50-53 ("It is a combined result of reduced tumor burden due to photothermal interactions ...") (emphasis added); column 13, lines 55-58 ("Clearly, the photothermal effect of the 808 nm diode laser on organized tissue can be greatly enhanced when the chromophore ICG with an absorption peak around 800 nm is used.") (emphasis added); column 13, line 61 to column 14, line 7 ("It is the ICG molecule, when injected to the target tissue, that absorbs strongly the 808 nm radiation and reaches an excited state. When the molecule returns to ground state, the stored energy is released in the form of heat which can be absorbed by surrounding tissue to elevate temperature. (The excited ICG molecule may also cause other biochemical reactions which may be the key in our induced immunological responses.) When a sufficient amount of ICG molecules are excited within a certain time (normally shorter than the tissue thermal relaxation time), the released heat can be absorbed by tissue cells faster than it can be dispersed. If the exposure to laser is long enough, the accumulated heat energy can raise tissue temperature to a level at which photothermal destruction of organized tissue can occur.") (emphasis added); and column 14, line 32-33 ("Of course, the destruction of tumor cells due to photothermal interaction was a predominant effect.") (emphasis added). Moreover, in the example section of the

'712 patent, it is clear that the photothermal effect is significant, sometimes leading to internal explosions. *See, e.g.*, column 12, lines 4-11 ("Almost all the tumors had temperature elevation immediately after the laser treatment. The ICG-H_2O or ICG-Chitosan solution injected tumors usually raised temperature by 40°F, while the ICG free tumor still raised temperature but at a lower level, usually 20° to 30°F above the body temperature depending on the laser power and duration."); and column 12, lines 14-15. This consistent teaching in the '712 patent leads the person of skill in the art to the conclusion that the photothermal effect is desirable, and in fact, critical to the success of the disclosed methods. Moreover, the claimed invention recites a chromophore being suitable to generate thermal energy. *See, e.g.*, claims 1 and 2. Applicants submit that the teachings of additional features of the chromophores does not alter or diminish the primary role of the photothermal effect taught in the '712 patent. Therefore, the combination of the '712 patent with references teaching compounds that do not result in appreciable heating of teaching would change the principle of operation of the '712 patent, and therefore such a combination fails to establish *prima facie* obviousness. *See* MPEP § 2143.01 ("If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." (citations omitted)).

Applicants respectfully submit that US Patent Nos. 6,149,671 and U.S. Patent 5,747,475 do nothing to rectify the deficiencies in the '712 patent as they are a continuation and continuation in part, respectively of the primary reference and retain the emphasis on the desirability of the photothermal effect.

When combined with the '712 patent, US Patent No. 5,149,527 has no additional teaching or disclosure regarding the use of green porphyrins that mediate cell destruction in the absence of appreciable tissue heating. In fact, this patent contains no disclosure regarding photodynamic therapy at all. Thus, while this patent discloses "tissue destroying protocol[s]", it fails to specifically motivate the skilled artisan to the use of the claimed methods.

US Patent Nos. 5,149,527, 5,579,554, 4,912,04, and 4,436,727 relate to various immunoadjuvants. None of these references discuss photodynamic therapy, or more particularly, green porphyrins. There is also the noticeable absence of teaching regarding combination therapeutic approaches, and therefore provide no additional substance to the '712 patent.

Applicants note that Fischer et al. fails to provide any teaching, disclosure, or suggestion related to the instant method. This reference discloses the treatment and subsequent light therapy of tumor cells mixed with whole blood *in vitro*. No *in vivo* experiment is performed, no immunoadjuvant is present, and, in fact, no mention of immune responsiveness is made. The references does state that "[t]heses results encourage further investigations concerning the use of photodynamic therapy for suppressing haematogenous dissemination." *See* page 27 (final line of abstract). However, this is quite plainly an invitation to try such experiments, and therefore does not teach, disclose, or suggest the claimed methods when combined with the '712 patent and the other cited references.

van Hillegersberg contains no teaching or suggestion that exogenous green porphyrins and immunoadjuvants are useful in treating tumors resulting from metastasis. Applicants note that the reference states that "[d]ifferences in metastases to the lung were statistically insignificant." See page 735, first full paragraph. In other words, tumors resulting from metastasis may (*e.g.*, lymph node growth) or may not (*e.g.*, lung tumor growth) be affected with the disclosed photodynamic therapy. At best, such disclosure is an invitation to try green porphyrins.

Karrer also fails to provide motivation to one of skill in the art to modify the '712 patent and the remaining cited references to result in the claimed methods. The abstract of Karrer cited by the Office discloses a single patient whose skin metastases where treated with indocyanine green, the same photosensitizer disclosed in the '712 patent. Therefore, in the absence of further disclosure, Karrer fails to provide motivation to use green porphyrins in the claimed methods.

Applicants respectfully submit that Lapeš discloses the use of a photosensitizer in the treatment of local recurrences of cancer. *See* page 205, Section 2, first paragraph. No mention is made of treatment of metastases other than a suggestion that photodynamic therapy may be effective for treatment of cutaneous metastases of breast cancer. *See* page 205, Section 1, first sentence. Again, at best, this is nothing more than an invitation to try such a treatment.

Finally, the '712 patent teaches away from the use of a photosensitizer that does not have a photothermal effect and therefore there is no motivation to combine its disclosure with that of the cited references related to porphyrins. Applicants note that the fact that an invention can be modified is insufficient to establish *prima facie* obviousness in the absence of a suggestion or motivation to make such a modification. MPEP § 2142.01. Any disclosure teaching away from the

claimed invention also must be considered in the obviousness analysis. *Id.* The remaining cited references when combined with the '712 patent do not result in the claimed methods. Therefore, the combination of references does not establish a *prima facie* case of obviousness. Finally, in the analysis of prior art references, it is improper to exercise hindsight to select bits and pieces from the references to create a motivation to modify that is not found in the references, but only in the applicant's disclosure. *In re Dow Chemical Co.* 5 U.S.P.Q.2d § 1529, 1531 (Fed. Cir. 1988). Simply stated, the suggestion or motivation to modify a reference must be found in the prior art and is clearly absent if such a modification changes the principle of operation of the prior art invention.

2. The combination of references fail to provide a reasonable expectation of success.

In the absence of any teaching, disclosure, or suggestion regarding the use of green porphyrins that do not generate appreciable heat when activated by light, the combination of references cannot provide a reasonable expectation of success for the modification required to result in the claimed invention. As discussed *supra*, the skilled artisan recognizes that small differences in activation wavelength can result in distinct therapeutic outcomes and that a method requiring a thermal effect is not readily interchangeable with a method that does not have or require a thermal effect.

In sum, in the absence of a motivation to combine the references and a reasonable expectation of success in references, the combination of cited references fails to establish *prima facie* obviousness.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Rejection Under Judicially-Created Doctrine of Obviousness-Type Double Patenting

Claims 1-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-21 and 28-33 of co-pending Application Serial No. 09/756,687. Applicants respectfully request this rejection be held in abeyance until such time that patentable subject matter is indicated.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding objection to the specification and the rejections of the claims and to pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 273012011100. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By _____
Laurie L. Hill, Ph.D.
Registration No.: 51,804
MORRISON & FOERSTER LLP
3811 Valley Centre, Suite 500
San Diego, California 92130
(858) 720-7955
Attorney for Applicant